Sarkar, Mohamadi

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<1>
Authors
Katiyar S. Thelma BK. Murthy NS. Hedau S. Jain N. Gopalkrishna V. Husain SA. Das BC.
Title
Polymorphism of the p53 codon 72 arg/pro and the risk of HPV type 16/18-associated cervical and oral cancer in India
Source
Molecular & Cellular Biochemistry. 252(1-2):117-124, 2003 Oct.
Abstract
Infection of high risk human papillomaviruses (HPVs) specifically the types 16 and 18 has been strongly implicated in the development of cervical cancer. The E6 oncoproteins of these high risk HPVs are known to bind and induce degradation of p53 tumour suppressor protein through the ubiquitin pathways. This degradation is controlled by a common polymorphism of the p53 gene encoding either a proline or an arginine at its codon 72 in exon 4. Recently, it has been demonstrated that the presence of homozygous arginine at codon 72 renders p53 about seven times more susceptible to E6-mediated proteolytic degradation as well as to cervical cancer than those with proline homozygotes or proline/arginine heterozygotes. In India, prevalence of HPV as well as cancers of the uterine cervix and the oral cavity are highest in the world. We have examined this allele-specific predisposition in cervical and oral cancer which is associated with HPV as well as in a non-HPV-linked cancer of the breast. We have carried out investigation in women comprising whole spectrum of cervical lesions with 128 HPV 16/18 positive and 35 HPV negative invasive cervical carcinomas and 34 cases of HPV (16/18) positive and 16 HPV negative cervical dysplasias (mild, moderate and severe) and 104 age-group-matched healthy women as controls. Additionally, we have analysed p53 Arg-Pro polymorphism in 13 high risk HPV positive and 31 HPV negative oral cancers along with 20 normal controls and 77 breast cancers with 41 age-matched healthy controls.

We observed more than two fold higher risk for homozygous arginine (chi(2) = 6.3, df = 2, p = 0.04; OR = 2.3; 95% CI: 1.08-5.16) for HPV 16/18-positive cervical carcinomas when comparison was made only between HPV positive cervical cancers and normal controls but most interestingly, no significant association either in the frequency of homozygous arginine or proline alleles or their heterozygotes could be observed when all the three groups i.e. HPV-positive, HPV-negative cervical cancers and controls were considered simultaneously. No difference was also observed for either arginine or proline polymorphism between women with precancerous lesions of the uterine cervix carrying HPV 16/18 infection and controls. Similarly, increased risk of oral or breast cancer could not be correlated with the polymorphism of arginine/proline allele.

Thus the interaction between HPV oncoproteins and the p53 gene polymorphism specifically, homozygous arginine at codon 72 appears to play no role in the development of either cervical or oral cancer and also it

can not serve as a biomarker for early identification of cervical, oral or breast cancer. [References: 56]
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<2>
Authors
Bairey O. Blickstein D. Stark P. Prokocimer M. Nativ HM. Kirgner I. Shaklai M.
Title
Serum CA 125 as a prognostic factor in non-Hodgkin's lymphoma
Source
Leukemia & Lymphoma. 44(10):1733-1738, 2003 Sep.
Abstract
Cancer antigen 125 (CA 125) is a glycoprotein expressed in normal tissues originally derived from coelomic epithelia such as peritoneum, pleura, pericardium, fallopian tubes and endometrium. Serum CA 125 levels are elevated in various benign and malignant conditions that involve stimulation of these tissues. Although elevated levels have been reported in patients with non-Hodgkin's lymphoma (NHL), its role as a prognostic factor remained uncertain. In this study, serum CA 125 levels were measured prospectively in 108 consecutive patients with NHL: at diagnosis in 106, in remission in 39 and at relapse in 7. Levels were elevated in 43% at diagnosis. This finding was associated with advanced disease stage, bulky tumors, bone marrow involvement, extranodal disease (in stages III and IV), occurrence of B symptoms, pleural or peritoneal effusions, high serum LDH levels, high serum beta2 microglobulin (beta2-M) levels, elevated International Prognostic Score, poor performance status and partial or no response to treatment. No difference in CA 125 level was found between the indolent and aggressive lymphomas. Serum CA 125 levels at diagnosis had strong association with event-free and overall survival ($p = 0.01$ and 0.003, respectively), with the patients with increased levels having worse survival. Patients with high CA 125 levels at diagnosis who achieved remission showed a significant decrease in CA 125 levels in remission. In conclusion, CA 125 is not only a reliable marker for staging and assessing tumor activity in NHL, elevated levels are also predictive of decreased survival. [References: 29]
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Authors
Ezzati M. Lopez AD.
Title
Estimates of global mortality attributable to smoking in 2000
Source
Lancet. 362(9387):847-852, 2003 Sep 13.
Abstract
Background Smoking is a risk factor for several diseases and has been increasing in many developing countries. Our aim was to estimate global and regional mortality in 2000 caused by smoking, including an analysis of uncertainty.

Methods Following the methods of Peto and colleagues, we used lung-cancer mortality as an indirect marker for accumulated smoking risk. Never-smoker

lung-cancer mortality was estimated based on the household use of coal with poor ventilation. Relative risks were taken from the American Cancer Society Cancer Prevention Study, phase II, and the retrospective proportional mortality analysis of Liu and colleagues in China. Relative risks were corrected for confounding and extrapolation to other regions.

Results We estimated that in 2000, 4.83 (uncertainty range 3.94-5.93) million premature deaths in the world were attributable to smoking; 2.41 (1.80-3.15) million in developing countries and 2.43 (2.13-2.78) million in industrialised countries. 3.84 million of these deaths were in men. The leading causes of death from smoking were cardiovascular diseases (1.69 million deaths), chronic obstructive pulmonary disease (0.97 million deaths), and lung cancer (0.85 million deaths).

Interpretation Smoking was an important cause of global mortality in 2000. In view of the expected demographic and epidemiological transitions and current smoking patterns in the developing world, the health loss due to smoking will grow even larger unless effective interventions and policies that reduce smoking among men and prevent increases among women in developing countries are implemented. [References: 31]

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<4>

Authors
Fally BN. Schlieman MG. Virudachalam S. Bold RJ.

Title
Schedule-dependent molecular effects of the proteasome inhibitor bortezomib and gemcitabine in pancreatic cancer

Source
Journal of Surgical Research. 113(1):88-95, 2003 Jul.

Abstract
Background. 26S proteasome inhibitors are a novel class of compounds entering clinical trials as a method to increase tumor sensitivity to standard chemotherapy. We determined the effect of alternate sequencing regimens of a proteasome inhibitor and gemcitabine on molecular and cellular responses in pancreatic cancer cells.

Materials and methods. MIA-PaCa-2 human pancreatic cancer cells were treated with the proteasome inhibitor bortezomib either before, simultaneously or following exposure to gemcitabine. Expression of the cell cycle proteins p21(WAF1/CIP1) and p27(KIP1), and the antiapoptotic protein BCL-2 were determined by Western blotting. Cell cycle changes and immediate or delayed induction of apoptosis were quantitated.

Results. Gemcitabine followed by bortezomib induced the greatest induction of apoptosis and long-term inhibition of cell growth. Bortezomib treatment led to accumulation of p21(WAF1/CIP1) and p27(KIP1) and decreased BCL-2; gemcitabine decreased p27(KIP1), induced BCL-2 and had no effect on p21(WAF1/CIP1). When these agents were given in combination or sequence, intermediate changes in these proteins were observed, and the alterations did not correlate with immediate or delayed induction of apoptosis.

Conclusions. Inhibition of the 26S proteasome following chemotherapy appears to be the most effective regimen, though changes in BCL-2, p21(WAF1/CIP1), p27(KIP1) do not necessarily correlate with the cellular effects when various sequences are examined. Therefore, these proteins may not be the most appropriate surrogate markers of efficacy of this regimen. These data provide the background for the development of the optimal regimen to be used in clinical trials. (C) 2003 Elsevier Inc. All rights

reserved. [References: 44]
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<5>
Authors
Garcia-Rostan G. Zhao HY. Camp RL. Pollan M. Herrero A. Pardo J. Ran W. Carcangiu ML. Costa J. Tallini G.
Title
ras mutations are associated with aggressive tumor phenotypes and poor prognosis in thyroid cancer
Source
Journal of Clinical Oncology. 21(17):3226-3235, 2003 Sep 1.
Abstract
Purpose : ras oncogenic activation has long been demonstrated in thyroid carcinomas of follicular cell derivation, but no consistent relationship has been shown between mutations and clinicopathologic features.

Materials and Methods: We analyzed H-, K-, and N-ras mutations by polymerase chain reaction-single-strand conformational polymorphism followed by DNA sequencing in 125 thyroid carcinoma specimens from 107 patients, to include tumors covering the entire spectrum of thyroid tumor differentiation.

Results: Mutations were identified in four (8.2%) of 49 well-differentiated carcinomas (WDCs; two [6.7%] of 30 of the tumors were papillary carcinomas, two [10.5%] of 19 of them were follicular carcinomas), in 16 (55.2%) of 29 poorly differentiated carcinomas (PDCs), and in 15 (51.7%) of 29 undifferentiated carcinomas, with a significant association between ras mutation and poorly or undifferentiated tumors (P < .001). Twenty-six (74.3%) of 35 patients with ras-mutated tumors died as a result of disease as opposed to 23 (31.9%) of 72 patients with tumors lacking the mutations. Among patients with differentiated thyroid carcinomas (WDC and PDC), 11 (55.0%) of 20 patients with mutated tumors died as a result of disease as opposed to nine (15.5%) of 58 patients with wild-type ras tumors, and the correlation was independent of tumor differentiation and stage (P = .016). K-ras codon 13 mutations (all with G-A nucleotide transitions resulting in Gly>Asp substitution) and single activating mutations in any of the ras genes were also independent predictors of poor survival in differentiated thyroid carcinomas (P = .027 and P = .007, respectively).

Conclusion: These findings demonstrate that ras mutations are a marker for aggressive cancer behavior and indicate a possible role of ras genotyping to identify thyroid carcinoma subsets associated with poor prognosis. (C) 2003 by American Society of Clinical Oncology. [References: 28]
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<6>
Authors
Jarmalaite S. Kannio A. Anttila S. Lazutka JR. Husgafvel-Pursiainen K.
Title
Aberrant p16 promoter methylation in smokers and former smokers with nonsmall cell lung cancer

Source
International Journal of Cancer. 106(6):913-918, 2003 Oct 10.
Abstract
Hypermethylation of cytosines in CpG-rich islands of the promoter regions of regulatory genes has been discovered as a common mechanism of gene silencing during carcinogenesis. We analysed 64 primary lung carcinomas for promoter methylation of the tumour suppressor genes (TSGs) p16 (p16(INK4a)/CDKN2A) and p14 (p14(ARF)) by methylation-specific PCR, in order to evaluate aberrant methylation as a potential biomarker for epigenetic alterations in tobacco-related lung cancer. Methylation of p 16 was observed in 34% (22/64) of the lung tumours examined. In particular, p16 methylation occurred in nonsmall cell lung cancer (NSCLC) only, with 41% (22/54) of the tumours being positive. The highest frequency was found in large cell carcinoma (5/7, 71%), followed by adenocarcinoma (9/25, 36%) and squamous cell carcinoma (7/21, 33%). Methylation of the p14 gene was less frequent in lung cancer (4/52, 8%). When association with tobacco smoking was analysed, 42% (21/50) of NSCLC from ever smokers exhibited p16 methylation. Interestingly, the analysis revealed a significantly higher risk of p 16 methylation in former smokers as compared to current smokers [odds ratio (OR) 5. 1; 95% confidence interval (CI) 1.3-22]. The difference was retained after adjustment for age (OR 3.7; 95% CI 0.9-17). The promoter methylation results were then combined with data on genetic alterations determined previously in the same set of tumours. This data similarly showed that p16 methylation in parallel with p53 gene mutation or p 14 methylation occurred more frequently in former smokers than in current smokers (44% vs. 14%; P = 0.035). Taken together, our data suggest that analysis of promoter methylation in TSGs may provide a valuable biomarker for identification of groups with an elevated risk of cancer, such as smokers and ex-smokers. (C) 2003 Wiley-Liss, Inc. [References: 45]
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<7>
Authors
Wang Q. Larson PS. Schlechter BL. Zahid N. Finnemore E. De Las Morenas A. Blanchard RA. Rosenberg CL.
Title
Loss of heterozygosity in serial plasma DNA samples during follow-up of women with breast cancer
Source
International Journal of Cancer. 106(6):923-929, 2003 Oct 10.
Abstract
We evaluated the potential utility of occult circulating tumor DNA as a molecular marker of disease in subjects previously diagnosed with breast cancer. Using 24 microsatellite markers located at sites of frequent loss of heterozygosity (LOH) or allele imbalance in breast cancer, we analyzed DNA from 16 primary tumors (Stage IIA or more advanced) and 30 longitudinally collected plasma specimens. Clinical data at the time of plasma collection were obtained. All 16 tumors were characterized by an individual pattern of LOH. LOH was detected in 12 of 30 (40%) plasma samples, taken from 8 of 14 (57%) subjects. However, the number of LOH in plasma was small (n = 15), and the mean proportion of LOH was much lower than in the tumors (0.05 vs. 032). Although infrequent, 12 of IS (80%) plasma LOH were concordant with abnormalities in the paired tumors, and the mean percent LOH was higher than in normal plasmas, suggesting that they were authentic tumor-derived abnormalities. We found, despite this, no association, between plasma LOH and tumor stage or clinical status at time of blood collection (i.e., LOH was as common in subjects with no evident disease as in those with evident disease). In addition, detection of LOH was not consistent between serial samples from S of I I subjects

(45%), despite stable clinical conditions. No asscciation with clinical outcome was evident, although the sample size was small. Microsatellite instability in plasma was infrequent, nonconcordant with paired tumor and inconsistent in serial samples. This pilot study suggests that identifying tumor-specific LOH in the plasma of breast cancer subjects may not be useful for detecting occult metastases or for monitoring disease. Other detection techniques may be more promising, but circulating tumor DNA may not be a sufficiently accurate reflection of breast cancer clinical status or tumor activity. (C) 2003 Wiley-Liss, Inc. [References: 35]

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<8>

Authors

Wu XF. Tortolero-Luna G. Zhao H. Phatak D. Spitz MR. Follen M.

Title

Serum levels of insulin-like growth factor I and risk of squamous intraepithelial lesions of the cervix

Source

Clinical Cancer Research. 9(9):3356-3361, 2003 Aug 15.

Abstract

Squamous intraepithelial lesions (SILs) are areas of precancerouts growth in the cervix that can be indicative of future cervical cancer. Insulin-like growth factors (IGFS) and their binding proteins (IGFBPs) have been implicated in cancer development. Recent studies have demonstrated that elevated plasma IGF-I levels are associated with increased risk of prostate, lung, colon, and breast cancers. In this case-control study, we analyzed the relationship between serum levels of IGF-I and IGFBP-3, and SILs of the cervix. The case patients were comprised of 267 women treated at The University of Texas M. D. Anderson Cancer Center Colposcopy Clinic in Houston, Texas for abnormal Pap smears. The clinic serves minority and economically disadvantaged women referred from the County Health Department clinics of Harris County, Texas. The control subjects were 238 healthy women receiving family planning and screening services at two Harris County Health Department clinics. Case patients with either high-grade or low-grade SILs had significantly higher serum levels of IGF-I, IGFBP-3, and molar ratios of IGF-I:IGFBP-3 than the control subjects did. IGF-I levels in the highest quartile were associated with significantly higher risk of SILs compared with the lowest quartile, independent of IGFBP-3 levels. The odds ratio for the fourth quartile of IGF-I level, relative to the first quartile, was 8.54 (95% confidence interval, 4.15-17.60; P < 0.0001) after adjustment for age, ethnicity, smoking status, and IGFBP-3 level. There was a dose-response relationship between risk of SILs and the level of IGF-I: as the level of IGF-I increased, so did the risk of SILs. In addition, the serum level of IGFBP-3 was significantly higher in case patients than in control subjects. However, after adjustment for. IGF-I, no relationship was evident between IGFBP-3 level and risk of SILs. Serum levels of IGF-I may be a useful biomarker for assessing risk of SIL development. [References: 40]

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